STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 102680

TO: Phyllis Spivack Location: 1/2d01 Art Unit: 1614 Friday, August 29, 2003 Case Serial Number: 10/055915	From: Mary Hale Location: Biotech/Chem Library CM1-1E01 Phone: 308-4258 Mary.Hale@uspto.gov

Search Notes

S arched-

Structure, had to modify after reviewing one hit and noticed nitrogen was missing from drawn structure.

S arched-

Synonyms for depression….

Searched- therap? Or treatment

Searched- inventor

(+)8-OH,DPAT activity. 5-HT and (+)8-OH,DPAT stimulated basal (35S)GTP-gamma-S binding to h5-HT1A membranes by > 2-fold, while (-)8-OH,DPAT, buspirone, OPC-14523, and NAN-190 displayed partial agonist efficacies. These drug effects were all blocked by WAY-100635, which was inactive on its own. The present data identify OPC-14523 as a partial agonist at rat and human 5-HT1A receptors.

L52 ANSWER 8 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
1997:235584 Document No.: PREV199799534787. Antidepressant effect of OPC-14523 in the forced swimming test in mice. Tottori, Katsura; Kikuchi, Tetsuro; Uwahodo, Yasufumi; Yamada, Sakiko; Oshiro, Yasuo; Koga, Nobuyuki. Third Tokushima Inst. New Drug Res., Otsuka Pharmaceutical Co. Ltd., Tokushima 771-01 Japan. Japanese Journal of Pharmacology, (1997) Vol. 73, No. SUPPL. 1, pp. 59P. Meeting Info.: 70th Annual Meeting of the Japanese Pharmacological Society Chiba, Japan March 22-25, 1997 ISSN: 0021-5198. Language: English.

=> del his y

Spivack
10/055915

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=> d l3 que stat;d l6 que stat;e "5ht1a"/cn
L1                STR
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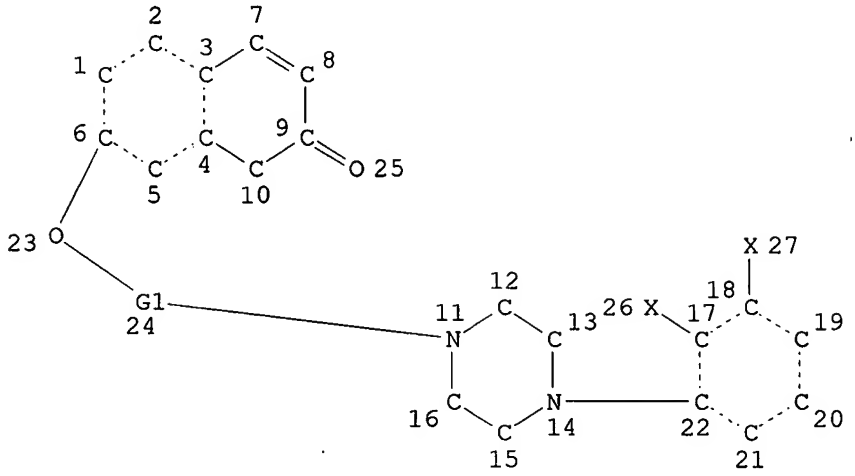

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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  27

STEREO ATTRIBUTES: NONE
L3             0 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED      1 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.02
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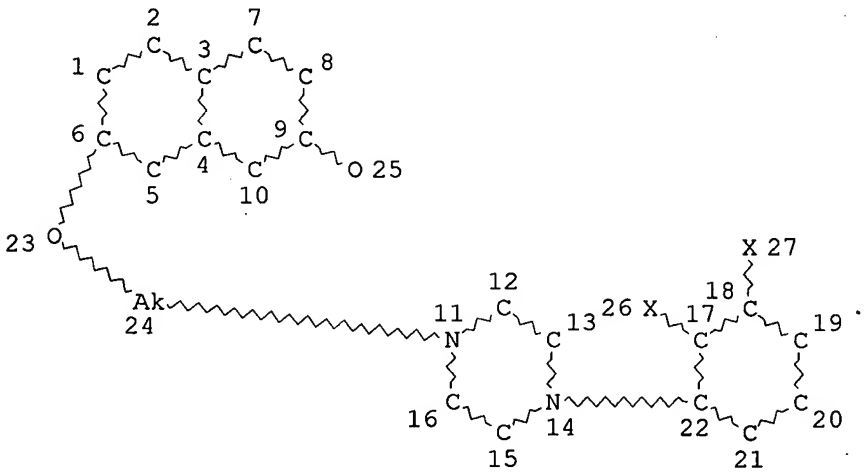

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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED


Searched by: Mary Hale 308-4258 CM-1 1E01
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GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 27

STEREO ATTRIBUTES: NONE
L6 0 SEA FILE=REGISTRY SSS FUL L4

100.0% PROCESSED 16840 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

E1 1 5HNM/CN
E2 1 5HS/CN
E3 0 --> 5HT1A/CN
E4 1 5I20AC/CN
E5 1 5I23/CN
E6 1 5I30/CN
E7 1 5IAF/CN
E8 1 5IUDR/CN
E9 1 5J11/CN
E10 1 5J16/CN
E11 1 5J18/CN
E12 1 5K0.4/CN

=> fil medl,hcaplus,biosis,embase,wpids

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	298.30	298.51

FILE 'MEDLINE' ENTERED AT 10:06:01 ON 29 AUG 2003

FILE 'HCAPLUS' ENTERED AT 10:06:01 ON 29 AUG 2003
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FILE 'EMBASE' ENTERED AT 10:06:01 ON 29 AUG 2003
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FILE 'WPIDS' ENTERED AT 10:06:01 ON 29 AUG 2003
COPYRIGHT (C) 2003 THOMSON DERWENT

=> s (5ht1a or 5ht?) and receptor
L7 1783 FILE MEDLINE
L8 4260 FILE HCAPLUS
L9 2777 FILE BIOSIS
L10 2077 FILE EMBASE
L11 578 FILE WPIDS

TOTAL FOR ALL FILES
L12 11475 (5HT1A OR 5HT?) AND RECEPTOR

=> s l12 and (treat? or therap? or prevent?) and (depress? or antidepress? or thymoanaleptic? or thymoleptic? or monoamine oxidase inhibit?)

Searched by: Mary Hale 308-4258 CM-1 1E01

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L13         143 FILE MEDLINE
L14         437 FILE HCAPLUS
L15         161 FILE BIOSIS
L16         209 FILE EMBASE
L17         283 FILE WPIDS

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                RESS? OR THYMOANALEPTIC? OR THYMOLEPTIC? OR MONOAMINE OXIDASE
                INHIBIT?)

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L19           0 FILE MEDLINE
L20           1 FILE HCAPLUS
L21           0 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L22           0 FILE EMBASE
L23           0 FILE WPIDS

TOTAL FOR ALL FILES
L24           1 L18 AND (JORDAN, S? OR JORDAN S? OR KIKUCHI T? OR KIKUCHI, T?)/A
                U,IN

=> d cbib abs

L24  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2003 ACS on STN
2002:594663   Document No. 137:150248  Carbostyril derivative 5-HT1a
     receptor agonists for treatment of central nervous
     system disorders.  Jordan, Shaun; Kikuchi, Tetsuro; Tottori,
     Katsura; Hirose, Tsuyoshi; Uwahodo, Yasufumi (Otsuka Pharmaceutical Co.,
     Ltd., Japan).  PCT Int. Appl. WO 2002060423 A2 20020808, 31 pp.
     DESIGNATED STATES: W:  AU, BR, CA, CN, ID, IN, JP, KR, MX, PH, SG; RW: AT,
     BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR.
     (English).  CODEN: PIXXD2.  APPLICATION: WO 2002-JP626 20020129.
     PRIORITY: US 2001-770210 20010129.
GI
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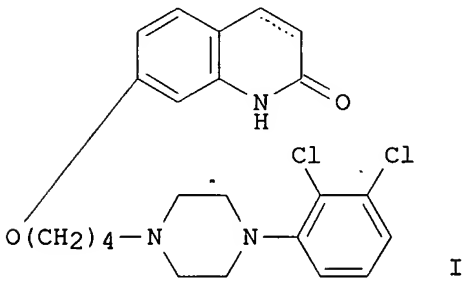


I

AB The invention discloses the use of a compd. for the prodn. of a medicament for **treating** a patient suffering from a disorder of the central nervous system assocd. with 5-HT1a **receptor** subtype, the medicament including as an active ingredient a carbostyril deriv. I (C-C bond between 3- and 4-positions in the carbostyril skeleton is single or double bond), or a pharmaceutically acceptable salt or solvate thereof.

Searched by: Mary Hale 308-4258 CM-1 1E01

=> fil reg
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	11.71	310.22

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-0.65	-0.65

FILE 'REGISTRY' ENTERED AT 10:08:56 ON 29 AUG 2003

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 27 AUG 2003 HIGHEST RN 574700-05-3
DICTIONARY FILE UPDATES: 27 AUG 2003 HIGHEST RN 574700-05-3

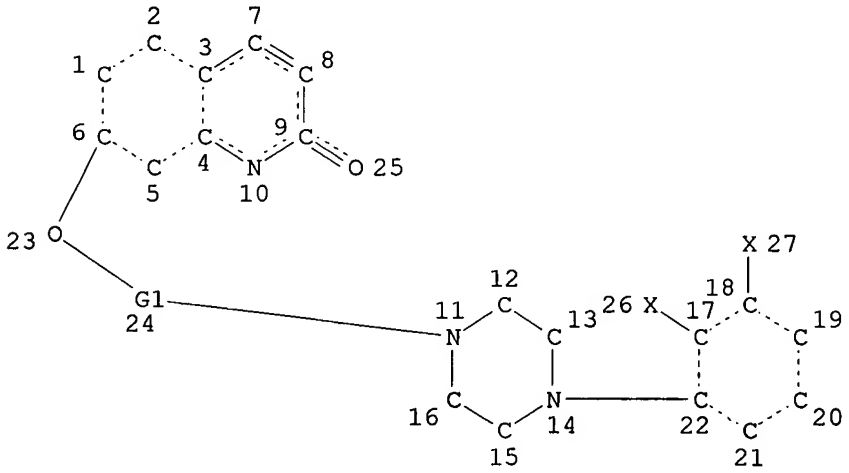
TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d l27 que stat
L25 STR



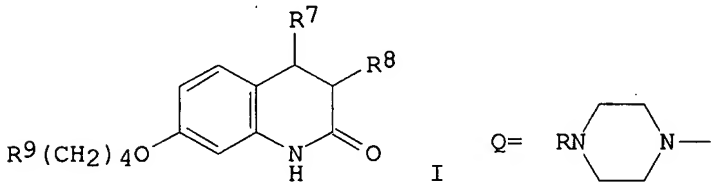
REP G1=(4-4) CH2
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 27

Searched by: Mary Hale 308-4258 CM-1 1E01

REFERENCE 4: 113:152468 Preparation and formulation of 7-[(4-phenylpiperazino)butoxy]carbostyrils as dopaminergic neurotransmitter antagonists. Oshiro, Yasuo; Sato, Seiji; Kurahashi, Nobuyuki (Otsuka Pharmaceutical Co., Ltd., Japan). Eur. Pat. Appl. EP 367141 A2 19900509, 27 pp. DESIGNATED STATES: R: CH, DE, ES, FR, GB, IT, LI, NL, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1989-120001 19891027. PRIORITY: JP 1988-276953 19881031.

GI



AB The title compds. (I; R7, R8 = H; R7R8 = bond; R9 = piperazino group Q; R = 2-alkoxyphenyl, 3,5- or 2,3-dichloro- or 2,3-dibromophenyl, 2-methyl-3-nitrophenyl, etc.) were prepd. Thus, 7-hydroxy-3,4-dihydrocarbostyril was refluxed 3 h with Br(CH2)4Br in aq. K2CO3 to give I (R7 = R8 = H, R9 = Br) which was refluxed 30 min with NaI in MeCN after which 1-(2,3-dichlorophenyl)piperazine was added and the whole refluxed 3 h to give I (R7 = R8 = H, R9 = Q, R = 2,3-Cl2C6H3) which had ED50 of 0.18 and >128 mg/kg orally for antiapomorphine and antiepinephrine activity, resp., in mice.

=> fil medl,hcaplus,biosis,embase,wpids

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	152.93	463.15

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-0.62	-1.27

FILE 'MEDLINE' ENTERED AT 10:10:49 ON 29 AUG 2003

FILE 'HCAPLUS' ENTERED AT 10:10:49 ON 29 AUG 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE 'BIOSIS' ENTERED AT 10:10:49 ON 29 AUG 2003

FILE 'EMBASE' ENTERED AT 10:10:49 ON 29 AUG 2003

FILE 'WPIDS' ENTERED AT 10:10:49 ON 29 AUG 2003

=> s (5(w)ht1a or 5(w)ht?) and receptor
L28 16340 FILE MEDLINE
L29 20077 FILE HCAPLUS

Searched by: Mary Hale 308-4258 CM-1 1E01

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L30       20558 FILE BIOSIS
L31       17574 FILE EMBASE
L32        1356 FILE WPIDS

TOTAL FOR ALL FILES
L33       75905 (5(W) HT1A OR 5(W) HT?) AND RECEPTOR

=> s l33 and (depress? or antidepress? or thymoanaleptic? or thymoleptic? or
monoamine oxidase inhibit?)
L34        2600 FILE MEDLINE
L35        3049 FILE HCAPLUS
L36        2962 FILE BIOSIS
L37        2858 FILE EMBASE
L38         750 FILE WPIDS

TOTAL FOR ALL FILES
L39       12219 L33 AND (DEPRESS? OR ANTIDEPRESS? OR THYMOANALEPTIC? OR THYMOLEP
                TIC? OR MONOAMINE OXIDASE INHIBIT?)

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L40           2 FILE MEDLINE
L41           4 FILE HCAPLUS
L42           6 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L43           2 FILE EMBASE
L44           2 FILE WPIDS

TOTAL FOR ALL FILES
L45          16 L39 AND (JORDAN, S? OR JORDAN S? OR KIKUCHI T? OR KIKUCHI, T?)/A
                U,IN

=> s l45 not l24
L46           2 FILE MEDLINE
L47           3 FILE HCAPLUS
L48           6 FILE BIOSIS
L49           2 FILE EMBASE
L50           2 FILE WPIDS

TOTAL FOR ALL FILES
L51          15 L45 NOT L24

=> dup rem l51
PROCESSING COMPLETED FOR L51
L52            8 DUP REM L51 (7 DUPLICATES REMOVED)

=> d cbib abs 1-8

L52  ANSWER 1 OF 8  HCAPLUS  COPYRIGHT 2003 ACS on STN DUPLICATE 1
2002:889556   Document No. 137:363096  Carbostyril derivative 5-
     HT1a receptor subtype agonist for treatment of central
     nervous system disorders.  Jordan, Shaun; Kikuchi, Tetsuro;
     Tottori, Katsura; Hirose, Tsuyoshi; Uwahodo, Yasufumi (USA).  U.S. Pat.
     Appl. Publ. US 2002173513 A1 20021121, 8 pp.  (English).  CODEN: USXXCO.
     APPLICATION: US 2002-55915 20020128.  PRIORITY: US 2001-PV331370 20010129.
GI
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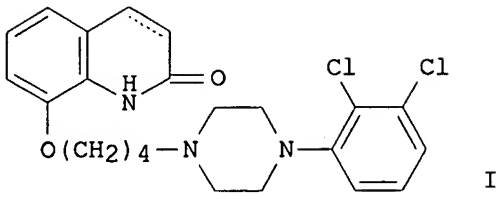
instant

Searched by: Mary Hale 308-4258 CM-1 1E01



I

AB The invention provides a method for treating a patient suffering from a disorder of the central nervous system assocd. with the **5-HT1a receptor** subtype, comprising as an active ingredient a carbostyril deriv. I (carbon-carbon bond between 3- and 4-positions in carbostyril skeleton is single or double bond), or a salt thereof.

L52 ANSWER 2 OF 8 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
AN 2002-682672 [73] WPIDS
AB WO 200260423 A UPAB: 20030723
NOVELTY - Disorders associated with **5-HT1A receptor** subtype are treated using carbostyril compound.

DETAILED DESCRIPTION - Disorders of the central nervous system associated with **5-HT1A receptor** subtype are treated using carbostyril compound of formula (I), its salt or solvate, in which the carbon-carbon bond between 3- and 4- positions in the carbostyril skeleton is a single or double bond.

ACTIVITY - Central nervous system-Gen.; **Antidepressant**; Vasotropic; Antialcoholic; Nootropic; Neuroprotective; Antiparkinsonian; Tranquilizer; Anorectic; Antimigraine; Neuroleptic.

MECHANISM OF ACTION - **5-HT1A receptor** subtype agonist. 7-(4-(4-(2,3-Dichlorophenyl)-1-piperazinyl)-butoxy)-3,4-dihydrocarbostyril (test compound)/serotonin (**5-HT**) (reference compound) was studied in triplicate at 10 different concentrations (0.01, 0.1, 1, 10, 50, 100, 500, 1000, 5000 and 10000 nm) to determine its displacement of (3H)8-OH-DPAT binding to h5-HT1A **receptors** in CHO cell membranes (15 - 20 micro g protein). Membranes (396 micro l) were incubated in 5 ml glass tubes containing (63H)8-OH-DPAT (396 micro l), test compound or vehicle (8 micro l) and buffer A (Tris.HCl (50 mM), MgSO4 (10 mM), EDTA (0.5 mM), ascorbic acid (0.1% w/v), pH = 7.4). All assays proceeded for 60 minutes at room temperature and were terminated by rapid filtration, using a harvester and ice-cold washes with buffer B (Tris HCl (50 mm); pH = 7.4). Non-specific binding was determined in the presence of (+)8-OH-DPAT (10 micro M). The test/reference compound showed following results: potency (EC50, nM; 95% confidence interval) = 2.12 (0.87 - 5.16)/3.67 (1.50 - 8.63); intrinsic agonist efficacy (Emax % plus or minus SEM) = 68.13 plus or minus 3.16/98.35 plus or minus 4.47; goodness of fit (r2) = 0.986/0.986.

USE - For treating disorders of the central nervous system associated with **5-HT1A receptor** subtype e.g. **depression** (including endogenous **depression**, major **depression**, melancholia or treatment-resistant **depression**); sexual dysfunction; alcohol abuse and drug addiction; cognitive impairments; neurodegenerative disease including Alzheimer's disease or Parkinson's disease; autism, Down's syndrome, panic, obsessive compulsive disorder (OCD), sleep disorders, emesis, motion sickness, obesity or migraine), attention deficit hyperactivity disorder; treatment-resistant schizophrenia, inveterate schizophrenia, or chronic schizophrenia with cognitive impairments, which fails to respond adequately to currently

available antipsychotic drugs (preferably drugs are chlorpromazine, haloperidol, sulpiride, fluphenazine, perphenazine, thioriodazine; pimozide, zotepine, risperidone, olanzapine, quetiapine or amisulpride; especially drugs are 1 - 3 (preferably 2) typical antipsychotic drugs selected from chlorpromazine, haloperidol) and perphenazine and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine and amisulpride) (all claimed).

ADVANTAGE - (I) Acts as a potent and highly safe drug therapy.

Dwg.0/0

L52 ANSWER 3 OF 8 MEDLINE on STN DUPLICATE 2

2002400655 Document Number: 22057738. PubMed ID: 12063084. The antipsychotic aripiprazole is a potent, partial agonist at the human **5-HT1A receptor**. **Jordan Shaun**; Koprivica Vuk; Chen Ruoyan; Tottori Katsura; **Kikuchi Tetsuro**; Altar C Anthony. (Neuroscience Department, Maryland Research Laboratories, Otsuka Maryland Research Institute, 9900 Medical Center Drive, Rockville, MD 20850, USA.. shaunj@otsuka.com) . EUROPEAN JOURNAL OF PHARMACOLOGY, (2002 Apr 26) 441 (3) 137-40. Journal code: 1254354. ISSN: 0014-2999. Pub. country: Netherlands. Language: English.

AB Aripiprazole, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butyloxy]-3,4-dihydro-2(1H)-quinolinone, a novel antipsychotic with partial agonist activity at dopamine D2 **receptors**, bound with high affinity to recombinant human **5-HT**(1A) **receptors** (h5-HT(1A)) in Chinese hamster ovary cell membranes and displayed potent, partial agonism at **5-HT**(1A) **receptors** in a guanosine-5'-O-(3-[(35)S]thio)-triphosphate ([(35)S]GTP gamma S)-binding assay that was blocked completely by a selective **5-HT** (1A) **receptor** antagonist. An interaction with **5-HT**(1A) **receptors** may contribute to the overall efficacy of aripiprazole against symptoms of schizophrenia, including anxiety, **depression**, cognitive and negative symptoms, and to its favorable side-effect profile. Combined with previous studies demonstrating the potent partial agonism of aripiprazole at dopamine D2 **receptors**, this study suggests aripiprazole is the first dopamine-serotonin system stabilizer.

L52 ANSWER 4 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

2003:293642 Document No.: PREV200300293642. BEHAVIORAL STUDIES OF OPC - 14523, A NOVEL **ANTIDEPRESSANT**: ANTI - STRESS AND ANTI - OBSESSIVE COMPULSIVE DISORDER (OCD) EFFICACY. Yamada, S. (1); Uwahodo, Y. (1); Tottori, K. (1); **Kikuchi, T. (1)**; Mori, T. (1). (1) Research Inst. of Pharmacological and Therapeutical Development, Otsuka Pharmaceutical Co., Ltd., Tokushima, Japan Japan. Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 307.6. http://sfn.scholarone.com. cd-rom. Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience Orlando, Florida, USA November 02-07, 2002 Society for Neuroscience. Language: English.

AB OPC-14523 is a novel compound with sigma and **5-HT1A** **receptor** agonistic and **5-HT** reuptake inhibitory activities, and shows **antidepressant**-like effects in animal models. In this study, we investigated the therapeutic and side-effect potential of OPC-14523 using animal models, and compared with those of selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, sertraline and paroxetine, and serotonin/noradrenaline reuptake inhibitors (SNRIs), such as venlafaxine and milnacipran.) OPC-14523 (30 and 100 mg/kg, p.o.) significantly inhibited abnormal eating behavior induced by tail-pinch stress in male Wistar rats, a putative model of bulimia nervosa. The inhibitory effect of OPC-14523 was partially antagonized by the sigma **receptor** antagonist NE-100, but not by

the **5-HT1A receptor** antagonist NAN-190.
SSRIs also reduced abnormal eating behavior, but SNRIs were inactive in this model. The anti-obsessive-compulsive disorder (OCD) effects were examined using marble-burying behavior in mice. OPC-14523 (30 and 100 mg/kg, p.o.), as well as SSRIs and SNRIs, significantly suppressed the number of marbles buried in sawdust. The suppression of marble-burying behavior was antagonized by NAN-190, but not by NE-100. In addition, we examined the effects of OPC-14523 on cognitive function using the Morris water maze. OPC-14523 did not impair spatial memory function, unlike fluoxetine.) These preclinical data predict that OPC-14523 may be effective in a broader range of psychiatric indications, including bulimia nervosa and OCD, without inducing cognitive dysfunction.

L52 ANSWER 5 OF 8 MEDLINE on STN DUPLICATE 3
2001700242 Document Number: 21615562. PubMed ID: 11747902.
Antidepressant-like responses to the combined sigma and **5-HT1A receptor** agonist OPC-14523. Tottori K; Miwa T; Uwahodo Y; Yamada S; Nakai M; Oshiro Y; **Kikuchi T**; Altar C A. (Research Institute of Pharmacological and Therapeutical Development, Otsuka Pharmaceutical Co., Ltd, 463-10 Kagasuno 771-0192, Kawauchi-cho Tokushima, Japan.. k_tottori@research.otsuka.co.jp) . NEUROPHARMACOLOGY, (2001 Dec) 41 (8) 976-88. Journal code: 0236217. ISSN: 0028-3908. Pub. country: England: United Kingdom. Language: English.

AB The **antidepressant**-like activity of a novel compound, OPC-14523, was investigated in comparison with the conventional **antidepressants**, fluoxetine and imipramine. OPC-14523 bound with nanomolar affinities to sigma **receptors** (IC(50)=47-56 nM), the **5-HT**(1A) **receptor** (IC(50)=2.3 nM), and the **5-HT** transporter (IC(50)=80 nM). OPC-14523 inhibited the in vitro reuptake of 3H-**5-HT** (IC(50)=27 nM), but it showed very weak inhibitory activity on 3H-NE and 3H-DA reuptake. OPC-14523 did not inhibit MAO A or B activities or muscarinic **receptors**. A single oral administration of OPC-14523 produced a marked **antidepressant**-like effect in the forced swimming test (FST) with rats (ED(50)=27 mg/kg) and mice (ED(50)=20mg/kg) without affecting the general locomotor activity. In contrast, fluoxetine and imipramine each required at least four days of repeated dosing to show this activity. The acute activity of OPC-14523 was blocked by pretreatment with the sigma **receptor** antagonist NE-100 or the selective **5-HT**(1A) **receptor** antagonist WAY-100635. The induction of flat body posture by OPC-14523 was blocked by the selective **5-HT**(1A) **receptor** antagonist NAN-190, and forebrain **5-HT** biosynthesis was attenuated by OPC-14523 at behaviorally effective doses. In contrast, OPC-14523, unlike fluoxetine, failed to inhibit **5-HT** reuptake at oral doses below 100mg/kg. Thus, the acute **antidepressant**-like action of OPC-14523 is achieved by the combined stimulation of sigma and **5-HT**(1A) **receptors** without inhibition of **5-HT** reuptake in vivo.

L52 ANSWER 6 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
2001:135108 Document No.: PREV200100135108. Role for sigma and **5-HT1A receptors** in the forced swimming test: supporting the mechanism of action of OPC-14523. Yamada, S. (1); Uwahodo, Y.; Tottori, K.; **Kikuchi, T.**; Altar, C. A.. (1) Otsuka Pharmaceutical Co. Ltd., Tokushima Japan. Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-871.7. print. Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience. ISSN: 0190-5295.

Searched by: Mary Hale 308-4258 CM-1 1E01

Language: English. Summary Language: English.

AB OPC-14523 is a novel synthetic compound with sigma and **5-HT1A receptor** agonistic activities and **5-HT** reuptake inhibitory activity. OPC-14523 has demonstrated **antidepressant**-like effects in the forced swimming test (FST) in rodents. The effect of OPC-14523 was almost completely antagonized by either a sigma **receptor** antagonist or **5-HT1A receptor** antagonists in the FST. Therefore, we further investigated the interaction between sigma and **5-HT1A receptors** in a modified version of Porsolt's rat FST. The immobility time of male Wistar rats was measured for 5 min using an auto activity analysis system. **5-HT** and 5-HIAA levels in the frontal cortex and hippocampus were measured after the FST. (+)-Pentazocine (10 mg/kg), a sigma 1 **receptor** agonist, or 8-OH-DPAT (0.1 mg/kg), a **5-HT1A receptor** agonist, significantly decreased immobility time in rat FST. The **5-HT1A receptor** antagonist WAY-100635 blocked the decrease in immobility time induced by 8-OH-DPAT, but did not affect the decrease in immobility time induced by (+)-pentazocine. The combination of (+)-pentazocine with 8-OH-DPAT further reduced immobility time in the FST compared to each treatment, indicating an additive effect of the two drugs. These data suggest that sigma and **5-HT1A receptors** independently exert **antidepressant**-like effects in the rat FST. Furthermore, these findings support prior evidence that the **antidepressant**-like effects of OPC-14523 are mediated by its agonistic activity at both sigma and **5-HT1A receptors**.

L52 ANSWER 7 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

2001:110538 Document No.: PREV200100110538. The **antidepressant** drug candidate OPC-14523 is a partial agonist at rat and recombinant human **5-HT1A receptors**. **Jordan, S. (1);** Koprivica, V.; Altar, C. A.. (1) Otsuka America Pharmaceut Inc, Rockville, MD USA. Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-387.13. print. Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience. ISSN: 0190-5295. Language: English. Summary Language: English.

AB OPC-14523 is in Phase II clinical trials in the USA for the treatment of **depression**. This drug binds with high affinity to **5-HT1A** (IC50 apprx 2 nM) and sigma **receptors** (IC50 apprx 30 nM), and its potent activity in rodent models predictive of **antidepressant** drug efficacy depends upon its **5-HT1A** and sigma **receptor** agonism. In vitro (35S)GTP-gamma-S binding methods were used to determine the intrinsic efficacy (relative to **5-HT**) of OPC-14523 at **5-HT1A receptors** in rat brain sections and at the human **5-HT1A receptor** (h5-HT1A) in CHO cell membranes. All reactions proceeded for 60 min at room temperature in a Tris-HCl buffer containing (35S)GTP-gamma-S, GDP and test drugs. Quantitative autoradiography and scintillation counting were used to measure (35S)GTP-gamma-S binding in transverse brain sections (20 mum) and h5-HT1A membranes, respectively. **5-HT** and 5-carboxyamidotryptamine (5-CT) stimulated basal (35S)GTP-gamma-S binding in **5-HT1A**/1B-containing brain regions by up to apprx75% and 95%, respectively. (+)8-OH,DPAT exhibited an intrinsic agonist efficacy of apprx85 % and partial agonist responses were produced by OPC-14523 and buspirone. These drug effects were all abolished by WAY-100635, which was inactive on its own. The partial agonist efficacy of OPC-14523 and buspirone was also evident in their inhibition of

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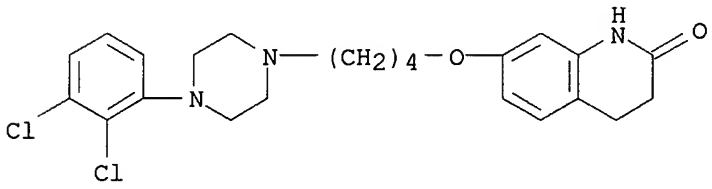
RN 129722-12-9 REGISTRY
CN 2(1H)-Quinolinone, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril
CN Abilitat
CN Aripiprazole
CN **OPC 14597**
CN OPC 31
FS 3D CONCORD
DR 156680-99-8
MF C23 H27 Cl2 N3 O2
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CIN, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

64 REFERENCES IN FILE CA (1937 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
68 REFERENCES IN FILE CAPLUS (1937 TO DATE)

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147 OPC
45 14523
L2 1 OPC 14523
(OPC(W)14523)

=> d l2

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
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CI COM
SR CA
LC STN Files: ADISINSIGHT, BIOSIS, CA, CAPLUS, CASREACT, DRUGNL, DRUGUPDATES, PHAR, PROMT, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL

The IALL format is the same as ALL with BIB ABS and IND indented, with text labels.

For additional information, please consult the following help messages:

HELP DFIELDS -- To see a complete list of individual display fields.
HELP FORMATS -- To see detailed descriptions of the predefined formats.
ENTER DISPLAY FORMAT (IDE):end

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L27 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
RN 129722-25-4 REGISTRY
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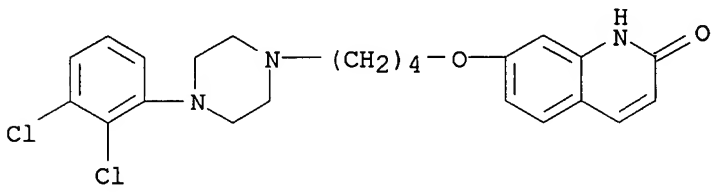
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



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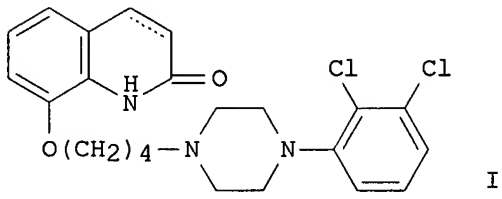
4 REFERENCES IN FILE CA (1937 TO DATE)
4 REFERENCES IN FILE CAPLUS (1937 TO DATE)

REFERENCE 1: 137:363096 Carbostyril derivative 5-HT1a receptor subtype agonist for treatment of central nervous system disorders. Jordan, Shaun; Kikuchi, Tetsuro; Tottori, Katsura; Hirose, Tsuyoshi; Uwahodo, Yasufumi (USA). U.S. Pat. Appl. Publ. US 2002173513 A1 20021121, 8 pp. (English). CODEN: USXXCO. APPLICATION: US 2002-55915 20020128. PRIORITY: US 2001-PV331370 20010129.

GI



I

AB The invention provides a method for treating a patient suffering from a disorder of the central nervous system assocd. with the 5-HT1a receptor subtype, comprising as an active ingredient a carbostyril deriv. I (carbon-carbon bond between 3- and 4-positions in carbostyril skeleton is

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single or double bond), or a salt thereof.

REFERENCE 2: 137:150248 Carbostyril derivative 5-HT1a receptor agonists for treatment of central nervous system disorders. Jordan, Shaun; Kikuchi, Tetsuro; Tottori, Katsura; Hirose, Tsuyoshi; Uwahodo, Yasufumi (Otsuka Pharmaceutical Co., Ltd., Japan). PCT Int. Appl. WO 2002060423 A2 20020808, 31 pp. DESIGNATED STATES: W: AU, BR, CA, CN, ID, IN, JP, KR, MX, PH, SG; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-JP626 20020129. PRIORITY: US 2001-770210 20010129.

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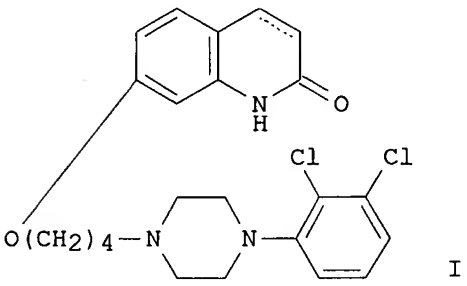

I

AB The invention discloses the use of a compd. for the prodn. of a medicament for treating a patient suffering from a disorder of the central nervous system assocd. with 5-HT1a receptor subtype, the medicament including as an active ingredient a carbostyril deriv. I (C-C bond between 3- and 4-positions in the carbostyril skeleton is single or double bond), or a pharmaceutically acceptable salt or solvate thereof.

REFERENCE 3: 128:175797 Novel Antipsychotic Agents with Dopamine Autoreceptor Agonist Properties: Synthesis and Pharmacology of 7-[4-(4-Phenyl-1-piperazinyl)butoxy]-3,4-dihydro-2(1H)-quinolinone Derivatives. Oshiro, Yasuo; Sato, Seiji; Kurahashi, Nobuyuki; Tanaka, Tatsuyoshi; Kikuchi, Tetsuro; Tottori, Katsura; Uwahodo, Yasufumi; Nishi, Takao (Third Institute of New Drug Research, Otsuka Pharmaceutical Company Ltd., Tokushima, 771-01, Japan). Journal of Medicinal Chemistry, 41(5), 658-667 (English) 1998. CODEN: JMCMAR. ISSN: 0022-2623. Publisher: American Chemical Society.

AB To develop a novel antipsychotic agent which is an agonist of dopamine (DA) autoreceptors and an antagonist of postsynaptic DA receptors, a series of 7-[4-[4-(substituted phenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1H)-quinolinones was synthesized and their dual activities were examd. The postsynaptic DA receptor antagonistic activities of the compds. were evaluated by their ability to inhibit stereotypy induced by apomorphine in mice, and the autoreceptor agonist activities were detd. by their effects on the .gamma.-butyrolactone (GBL)-induced increase in L-dihydroxyphenylalanine (DOPA) synthesis in the mouse brain. Many compds. inhibited the stereotypic behavior, and several compds. reversed the GBL-induced increase in the DOPA synthesis. Among them, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1H)-quinolinone (aripiprazole, OPC-14597) (I) had these 2 activities. This compd. reversed the GBL-induced DOPA synthesis (ED50 values of 5.1 .mu.mol/kg po) and inhibited the APO induced stereotypy (ED50 values of 0.6 mmol/kg po). I induced catalepsy at 10-fold higher dose than that required for the antagonism of APO-induced stereotypy (ED50 value of 7.8 .mu.mol/kg oral).

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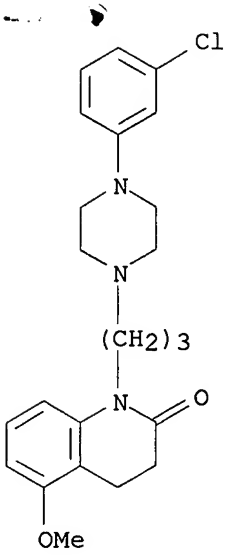

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

6 REFERENCES IN FILE CA (1937 TO DATE)
6 REFERENCES IN FILE CAPLUS (1937 TO DATE)

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FILE 'HOME' ENTERED AT 17:38:20 ON 20 SEP 2003

=> e registy
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
The EXPAND command is used to look at the index in a file
which has an index. This file does not have an index.

=> s POC 14597
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Some commands only work in certain files. For example, the EXPAND
command can only be used to look at the index in a file which has an
index. Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of
commands which can be used in this file.

=> file registy
'REGISTY' IS NOT A VALID FILE NAME
SESSION CONTINUES IN FILE 'HOME'
Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files
that are available. If you have requested multiple files, you can
specify a corrected file name or you can enter "IGNORE" to continue
accessing the remaining file names entered.

=> s OPC 14597
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Some commands only work in certain files. For example, the EXPAND
command can only be used to look at the index in a file which has an
index. Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of
commands which can be used in this file.

=> file registry
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.42	0.42

FILE 'REGISTRY' ENTERED AT 17:39:26 ON 20 SEP 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP
PROPERTIES for more information. See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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L1          1 OPC 14597
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=> d l1

L1 ANSWER 1 OF 1 REGISTRY